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(54) Medical device

(57) The invention relates to a medical device useful for the localized delivery of a therapeutic agent having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent. Preferred devices include a structure including a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of the porous polymeric material. Methods for making a medical device having a blood-contacting surface are also provided. One method includes the use of a concentrating agent whereby to localise the therapeutic agent within the porous material. Another method involves multiple immersion steps without the use of a concentrating agent.

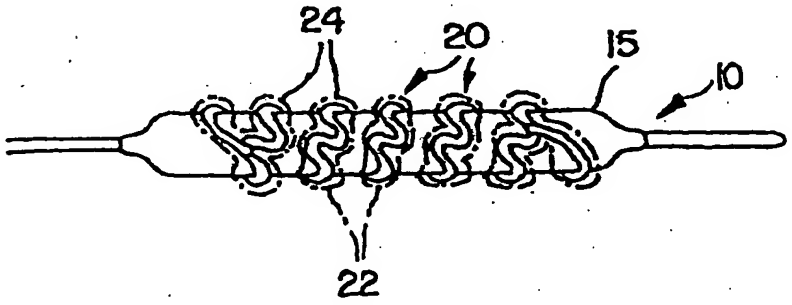

FIG. 1

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7. A medical device as claimed in any preceding claim wherein said therapeutic agent comprises an antithrombotic material.

8. A medical device as claimed in claim 7 wherein the antithrombotic material is heparin, a heparin derivative or analog.

9. A medical device as claimed in any of one of claims 1 to 6 wherein said therapeutic agent is a peptidic drug.

10. A medical device as claimed in any preceding claim having a generally cylindrical or sheet-like shape.

11. A medical device as claimed in any preceding claim comprising a catheter, a stent, or a guide wire.

12. A medical device as claimed in claim 11 comprising an intralumenal stent.

13. An intralumenal stent comprising:

a generally cylindrical stent body; and
an adherent layer on the stent body comprising a porous polymeric material and an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of the porous polymeric material.

14. A method for making a medical device, said method comprising the steps of:

(a) providing a structure comprising a porous material;
(b) contacting said structure with a concentrating agent whereby to disperse the concentrating agent throughout at least a portion of the porous material;
(c) contacting said structure comprising a porous material and the concentrating agent with a solution of a therapeutic agent; and
(d) removing the therapeutic agent from solution within the porous material at the locations of the concentrating agent.

15. A method as claimed in claim 14 wherein said concentrating agent is selected from the group of a binding agent, a sequestering agent, a nucleating agent, a seed crystal, or a combination thereof.

16. A method as claimed in claim 14 or claim 15 wherein step (d) is effected by reducing the temperature, changing the pH or changing the ionic strength of the solution of the therapeutic agent.

17. A method for making a medical device, said method comprising the steps of:

(a) providing a structure comprising a porous material;
(b) immersing said structure in a saturated solution of a therapeutic agent for a sufficient period of time to allow the solution to fill the porous material;
(c) removing the structure from the solution;
(d) drying the structure; and
(e) repeating steps (b) through (d) whereby to provide a therapeutic agent dispersed within the porous material.

18. A method as claimed in claim 17 further comprising a step of removing air bubbles from the porous material while immersed in the solution of the therapeutic agent.

19. A method as claimed in claim 18 wherein the step of removing air bubbles from the porous material is effected by applying ultrasonics, reduced pressure, elevated pressure, or a combination thereof, to the solution.

20. A method as claimed in any one of claims 14 to 19 further comprising the step of applying an overlayer of a polymer to said structure.

21. A method as claimed in any one of claims 14 to 20 wherein said porous material is a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, or a combination of two or more of these materials.

22. A method as claimed in any one of claims 14 to 21 wherein said therapeutic agent is an antithrombotic material.

23. A medical device obtainable by a process as claimed in any one of claims 14 to 22.

24. A substrate having at least one blood-contacting surface as defined in any one of claims 1 to 9.

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EUROPEAN SEARCH REPORT

Application Number
EP 99 30 3427

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	18 July 2001	Kuehne, H-C

CATEGORY OF CITED DOCUMENTS

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The present search report has been drawn up for all claims

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swelling biostable" or "non-swellable biostable" polymer is one that does not absorb a significant amount of water (i.e. it absorbs less than about 10% by weight water) and it is not readily degraded in the body. Such non-swelling biostable polymers include, for example, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, and combinations thereof. If the polymer is biodegradable, the rate at which it degrades is slower than the rate at which the therapeutic agent elutes.

[0030] If the porous material is in the form of a porous sheet (i.e. film) or coating, it can be made by a variety of methods. These methods can include, for example, using a solid particulate material (also referred to herein as pore-forming material) that can be substantially removed after the film or coating is formed, thereby forming pores. By using a solid particulate material during film or coating formation, the size of the pores can, to some extent, be controlled by the size of the solid particulate material being used. The particulate material can range from less than about 1 μm in diameter to about 1000 μm, preferably from about 1 μm to about 100 μm, more preferably about 5 μm to about 50 μm. For uniformity of pores, the particulate material can be screened through successively finer mesh sieves, e.g. through 100, 170, 270, 325, 400, and 500 mesh analytical grade stainless steel mesh sieves, to produce a desired range of particle sizes.

[0031] The particulate material may include inorganic and organic particulate material, including, for example, sodium chloride, lithium chloride, sucrose, glucose, sorbitol, sodium citrate, sodium ascorbate, urea, citric acid, dextran, poly(ethylene glycol), sodium nitroprusside, mannitol, sodium bicarbonate, ascorbic acid, sodium salicylate, or combinations thereof. It will be understood by one of skill in the art that a mixture of different particulate materials can be used if desired. Also, it will be understood by one of skill in the art that because a portion of the particulate material may remain within the film, it is preferred that the solid particulate material be biocompatible.

[0032] Typically, the particulate material chosen is less soluble than the polymer in the chosen solvent (e.g. water or an organic solvent) used to deposit or form the polymer. The particulate material may actually be soluble in the solvent; however, to form pores, it only has to be less soluble than the polymer in the solvent of choice. As the solvent is removed from the solution, the pore-forming material will precipitate out of solution and form particles surrounded by the polymer, which is still in solution. The polymer will then come out of solution as more solvent is removed and the particles will be dispersed within the polymer. After the solvent is removed, the particulate material is removed using a liquid in which the polymer is not soluble, thereby forming pores.

[0033] In one method according to the present invention, a porous sheet material (e.g. polyurethane sheet material) can be made by dissolving a polymer (e.g. polyether urethane) in an organic solvent (e.g. 1-methyl-2-pyrrolidone); mixing into the resulting polymer solution a crystalline, particulate material (e.g. sodium chloride, sucrose, etc.) that is not soluble in the solvent; casting the solution with particulate material into a thin film; and then applying a second solvent (e.g. water), to dissolve and remove the particulate material, thereby leaving a porous sheet. Such a method is disclosed in US-A-5,591,227 (Dinh et al.) and US-A-5,599,352 (Dinh et al.).

[0034] Preferably, a combination of soluble and insoluble particulate material may be used to create a broader range of pore sizes. The use of a soluble particulate material, such as poly(ethylene glycol), may create small (< 2 μm diameter) interconnecting pores that create a solvent path for the removal of the larger (e.g. 50 μm diameter) particles, which may not be in particle-to-particle contact.

[0035] A suspension of particulate material may be created by first dissolving the particulate in a solvent, then precipitating the mixture in a solution of polymer in a second solvent in which the particulate is insoluble. For example, an 8% solution of sodium nitroprusside in ethanol can be added with rapid stirring to a 2% solution of polyurethane in tetrahydrofuran. The sodium nitroprusside precipitates to form a suspension of less than about 5 μm particles.

[0036] The weight ratio of pore-forming material to polymer in a coating composition may range from about 1:3 to about 9:1, preferably about 2:1 to about 9:1, although this is not necessarily limiting. In theory, the porosity is limited by the toughness of the polymer.

[0037] A smooth coating may be obtained by applying an atomized spray to the stent. The spray should be applied at a rate such that evaporation prevents the accumulation of sufficient liquid to form drips along the stent. A macroscopically smooth surface may also be obtained by keeping the particle size less than about ¼ of the coating or film thickness.

[0038] Although films (i.e. sheet materials) for medical devices, particularly stent bodies, according to the present invention can be manufactured separately from the support structure of the medical device and attached to the support structure after formation, preferred methods include forming the films directly on the support structure such that the support structure is at least partially, preferably completely, encapsulated by the film (i.e. sheet material).

[0039] Alternatively, medical devices can include a coating of a porous polymer made by spraying a solution of the polymer and particulate material directly on the support. In this way, the coating does not necessarily form a film that encapsulates the device; rather it forms a coating around the structure (e.g. wire) of the device. The geometry of the porous material (coated wires vs. sheets or films) depends on the coating substrate and is largely independent of the pore forming and application methods used. A film can be made by spraying, dip-

ping, or sheet. casting, as long as the mandrel is a rod or a flat sheet. The stent wires can be coated by any of these methods as well, although most preferably, they are coated by spraying to prevent droplet formation.

[0040] In one such method, which is disclosed in WO 97/07973 (Medtronic, Inc.), a stent is placed on a mandrel. A particulate material is then applied to the mandrel and stent such that it is lightly adhered to the mandrel. The particulate material should be readily soluble in a solvent which will not also dissolve the polymer chosen for the film. For example, crystalline sodium bicarbonate is a water soluble material that can be used as the particulate material. A non-aqueous liquid, preferably a solvent for the polymer film material, can be applied to the mandrel before applying the particulate material in order to retain more of the particulate material on the mandrel. For example, when a polyurethane is to be used for the film material, the solvent 1-methyl-2-pyrrolidinone (NMP) can be used to wet the surface of the mandrel before the application of particulate material. Preferably, the mandrel is completely dusted with the particulate in the portions of the mandrel to be coated with the polymer film. This can be accomplished by dipping the mandrel in NMP, allowing it to drain vertically for a few seconds and then dusting the sodium bicarbonate onto the mandrel while rotating it horizontally until no further bicarbonate particles adhere. Excess particulate material can be removed by gently tapping the mandrel.

[0041] Coating with polymer may proceed immediately following application of the particulate material. A polymer is provided in a dilute solution and is applied to the particle-coated stent and mandrel. For example, polyurethane can be dissolved in NMP to make a 10% solution. Gel particles and particulate impurities can be removed from the solution by use of a clinical centrifuge. The polymer solution can be applied by dipping the mandrel into the solution and letting the solvent evaporate. With the solution of polyurethane and NMP, a single dip in the solution can provide a film of adequate thickness. To assist in the formation of communicating passageways through the polymer between the blood-contacting surface and the lumen-contacting surface, additional sodium bicarbonate particles are preferably dusted onto the polymer solution immediately after the dipping operation and before the polymer solution has dried. Excess particulate material can be removed by gently tapping the mandrel. To precipitate and consolidate the polyurethane film on the stent, it can be dipped briefly (about 5 minutes) in water and then rolled gently against a wetted surface, such as a wet paper towel. The stent assembly can then be placed into one or more water baths over an extended period (e.g. 8 hours) to dissolve and remove the sodium bicarbonate. After drying in air at temperatures from about 20°C to about 50°C, the film can then be trimmed to match the contour of the wire.

[0042] In yet another method, a solvent in which the polymer is soluble that is capable of phase separating from the polymer at a reduced temperature can be used to prepare a porous polymer film. In this method, the stent or other medical device is placed in a cavity of a mold designed for forming a film around the stent, similar to that disclosed in US-A-5,510,077 (Dinh et al.). A solution of the desired polymer, such as polyurethane, dissolved in a solvent, such as dioxane, is added to the mold. The temperature of the solution is then reduced to a temperature at which the solvent freezes and phase separates from the polymer, thereby forming particulate material (i.e. frozen solvent particles) *in situ*. Typically, for polyurethane in dioxane, this is a temperature of about -70°C to about 3°C. The composition is then immersed in an ice cold water bath (at about 3°C) for a few days to allow the dioxane to dissolve into the ice cold water, thereby forming pores. The number and size of the pores can be controlled by the concentration of the polymer and the freezing temperature. A method similar to this is disclosed in Liu et al., J. Biomed. Mater. Res. 26: 1489, 1992. This method can be improved on by using a two-step freezing process as disclosed in U. S. Pat. Application. Ser. No. 09/069,659, filed on April 29, 1998.

[0043] In yet another embodiment, a porous material can be created from a mixture of a low boiling good solvent and a higher boiling poor solvent, in which the polymer is soluble. After application to the target substrate, the lower boiling good solvent evaporates preferentially until a point is reached where the polymer precipitates from the remaining solvent mixture, which is relatively richer in the poor solvent. The polymer precipitates in and around pockets of the poor solvent, creating a porous structure. The number and size of pores can be controlled by the boiling points of the two solvents, the concentration of polymer and the drying rate. An example is a 1% solution of poly(1-lactic acid) (PLLA) in a 60:40 mixture of chloroform:iso-octane. As the chloroform evaporates, the PLLA precipitates from the iso-octane to create an opaque PLLA coating containing 2-5 µm pores. This method is further described in US-A-5,679,400 (Tuch).

[0044] The therapeutic agent used in the present invention may be any therapeutic agent which possesses desirable therapeutic characteristics and which can be provided in a form that can be solubilized, for example, by water or an organic solvent, and are capable of being eluted from the porous polymeric material in the body of a patient. Preferred therapeutic agents are solids, gels, or neat liquids (i.e. materials not dissolved in a solvent) at ambient temperature (i.e. about 20-25°C), and preferably at body temperatures, that are capable of being eluted from the porous polymeric material in the body of a patient. For example, antithrombotics, antiplatelet agents, antimitotic agents, antioxidants, antimetabolite agents, anti-inflammatory agents, enzyme inhibitors, and anti-angiogenic factors as disclosed in US-A-5,716,981 (Hunter et al.) could be used. Anticoagulant agents, such as heparin, heparin derivatives, and heparin analogs, could also be used to prevent the for-

mation of blood clots on the device.

[0045] A structure having a porous material, preferably a porous polymeric material, can be loaded with one or more therapeutic agents using a wide variety of methods. For example, the porous material can be immersed in a solution or dispersion of the therapeutic agent in a solvent. The solution (preferably, a supersaturated solution) or dispersion is allowed to fill the pores and the solvent is allowed to evaporate leaving the therapeutic agent dispersed within at least a portion of the pores. The solvent can be water or an organic solvent that does not dissolve the polymer. If the solvent does not dissolve the therapeutic agent, the particles of the therapeutic agent are smaller than the pore openings. Alternatively, in certain embodiments, the solvent can be chosen such that it swells the polymer, thereby achieving a greater level of incorporation of the therapeutic agent.

[0046] The following methods for loading one or more therapeutic agents into porous material are improved over prior art methods, such as spray coating methods. Although the same amount of therapeutic agent can be loaded onto a medical device, significantly less (e.g. about 100x less) waste of the therapeutic agent occurs using the following methods. This is particularly important for expensive therapeutic agents, such as peptidic drugs.

[0047] In one embodiment of the invention, filling of the pores can be enhanced through the use of ultrasonics, vacuum, and/or pressure. While the device is submerged in solution, ultrasonic energy or vacuum can be used to accelerate the removal of air bubbles from the pores allowing the pores to fill with the solution containing the therapeutic agent. Hyperbaric pressure on the solution may cause the air in the pores to be dissolved in the solution, thereby allowing the pores to fill with liquid. Furthermore, the level of incorporation can be increased by using multiple dip-vacuum-dry cycles. If the therapeutic agent saturates the solution by 10% by volume, for example, when the solvent evaporates the pores will be 10% filled with the agent. Repeating the cycle will fill the remaining 90% void space and fill an additional 9% of the original pore volume. Further cycles continue the trend. For this procedure to be effective, however, the solution is saturated so that the previously deposited agent does not dissolve in subsequent cycles.

[0048] Preferably, a method of the invention includes loading a structure comprising a porous material with a concentrating agent, which may be a precipitating agent (e.g. a binding agent, sequestering agent, nucleating agent, etc.), a seed crystal, or the like, dispersed throughout at least a portion, preferably, a substantial portion, of the porous material, and subsequently loading the structure comprising a porous material and the concentrating agent with a solution of a therapeutic agent, wherein the therapeutic agent is removed from solution (e.g. as by crystallization and/or precipitation) within the porous material at the locations of the concentrating agent. This is a significantly improved method in that the concentrating agent provides a driving force for localization of the drug within the pores of the polymer. That is, it is believed that the concentrating agent provides a thermodynamically favourable surface for crystallization or precipitation.

[0049] The concentrating agent can be a precipitating agent or a seed crystal, for example, or any substance that can cause the therapeutic agent to fall out of solution. As used herein, a seed crystal is a solid material that is the same as the therapeutic agent being deposited. As used herein, a precipitating agent is a solid material that is different from the therapeutic agent being deposited. It can include, for example, materials that have a particular affinity for the therapeutic agent of interest, such as binding agents, sequestering agents, nucleating agents, and mixtures thereof. Examples of sequestering agents include heparin to sequester heparin, binding growth factors such as bFGF and, for example, cyclodextrins to trap appropriately sized therapeutic agents to fit in their ring structures. Examples of binding agents include polycations (e.g. protamine) and polyanions (e.g. heparin sulfate) for binding anionic and cationic therapeutic agents, respectively. The binding agent can also include a counterion of a salt that is insoluble upon complexation with the therapeutic agent in the solvent used in the solution of the therapeutic agent.

[0050] The solution containing the therapeutic agent is preferably a supersaturated solution, although this is not a necessary requirement. This can be prepared at elevated temperatures taking into consideration the limits of stability of the therapeutic agents and the porous material. The porous polymeric material with concentrating agent therein can be immersed in a solution of the therapeutic agent in a solvent. The solution is allowed to fill the pores and the therapeutic agent allowed to come out of solution (e.g. as by the formation of crystals). The solvent can be water or an organic solvent that does not dissolve the porous polymer, although it may swell the polymer as described above. The choice of solvent is one that is compatible with the therapeutic agent and porous material of choice. Filling of the pores can be enhanced through the use of ultrasonics, vacuum, and/or pressure, as well as by using multiple dip-vacuum-dry cycles, as described above.

[0051] Crystal and/or precipitate formation can be initiated by a variety of mechanisms. They may spontaneously form. by a variety of mechanisms. They may spontaneously form. Alternatively, the solution of the therapeutic agent within the pores may need to be cooled to initiate crystallization and/or precipitation. It may be possible to initiate crystallization and/or precipitation by changing the pH and/or ionic strength of the solution of the therapeutic agent within the pores.

[0052] The initial concentrating agent, which may be a solid, liquid, or a gel, can be placed in the pores of the porous material by a variety of methods. For example, if the concentrating agent is a seed crystal of the thera-

peutic agent of interest, immersing the porous material in a solution or dispersion of the therapeutic agent in a solvent, allowing it to fill the pores, and allowing the solvent to evaporate, provides the therapeutic agent dispersed within at least a portion of the pores, as described above. Similarly, if the concentrating agent is a precipitating agent, the porous material can be immersed in a solution of this agent.

[0053] The methods of the present invention are advantageous in that the structure can be loaded with the therapeutic agent *in situ*, i.e. at or near the point of therapeutic use, typically before administration, preferably implantation, to a patient. This is particularly useful because the device can be stored and transported prior to incorporation of the therapeutic agent. This feature has several advantages. For example, the relevant consumer can select the therapeutic agent to be used from a wider range of therapeutic agents. Thus, the therapeutic agent selected is not limited to only those supplied with the device but can instead be applied according to the therapy required.

[0054] In order to provide additional control over the elution of the therapeutic agent, an overlayer may be applied to the medical device, as is disclosed in US-A-5,679,400 (Tuch), US-A-5,624,411 (Tuch), and US-A-5,624,411 (Tuch). The overlayer, typically in the form of a porous polymer, is in intimate contact with the therapeutic agent and allows it to be retained on the medical device. It also controls the administration of the therapeutic agent following implantation. For a stent, an overlayer is particularly desirable to retain the therapeutic agent on the stent during expansion of the stent.

[0055] The invention will now be described further by way of illustration with reference to the following non-limiting example and to the accompanying drawings, in which:

Figure 1 is an elevational view of one embodiment of a device according to the invention with a balloon catheter as a mode of delivery of the device; and
Figure 2 is an elevational view of another embodiment of a device according to the invention with a balloon catheter as a mode of delivery of the device.

[0056] In the Example which follows, all parts, percentages, ratios, etc. are by weight unless otherwise indicated.

Example

[0057] Wiktor stents were coated as follows: 4 g of a 5 wt% solution of polyurethane as disclosed in US-A-4,873,308 (Coury et al.) in tetrahydrofuran (THF) and 20 g of a 5 wt% solution of citric acid in THF were combined and sprayed onto wiktor stents using an air brush, similar to the method disclosed in US-A-5,679,400 (Tuch). Citric acid was extracted with deionized water for 10 minutes. The stent was then air dried at ambient temperature and weighed. The porous polyurethane coating eights were 0.5-0.7 mg.

[0058] Into a microcentrifuge tube was added 0.12 g tissue factor pathway inhibitor (TFPI) and 1.0 ml sterile water. This was agitated to dissolve the TFPI. The polyurethane coated stents were immersed in the TFPI solution, which was subjected to reduced pressure (28 inches (94.8 kPa) of Hg) to evacuate the air from the pores. The stents were air dried and the immersion/vacuum process was repeated twice. After the last immersion process, stents were air dried at ambient temperature for 20 minutes. Each stent was immersed for less than two seconds in deionized water to remove TFPI on the surface of the stents. The stents were then dried in ambient temperature under vacuum for about 12 hours. The stents were weighed to determine the amount of TFPI loaded into the pores, which ranged from 0.15 mg to 0.33 mg.

[0059] Half the stents were overcoated with a 2 wt% solution of polyurethane solution in THF using the spray coating method described above, resulting in a coating weight of 0.6 mg. These stents were tested for elution. The stents with the overcoating eluted more slowly than the stents without the overcoating.

Claims

1. A medical device having at least one blood-contacting surface comprising a porous material having dispersed therein an elutable therapeutic agent.

2. A medical device as claimed in claim 1 having at least one blood-contacting surface comprising:

   a porous polymeric material; and
   an elutable therapeutic agent in the form of a solid, gel, or neat liquid, which is dispersed in at least a portion of said porous polymeric material.

3. A medical device as claimed in claim 1 or claim 2 wherein said porous material comprises a film.

4. A medical device as claimed in claim 1 or claim 2 wherein said porous material comprises an integral portion of the device.

5. A medical device as claimed in any one of claims 1 to 4 wherein said porous material is a natural hydrogel, a synthetic hydrogel, silicone, polyurethane, polysulfone, cellulose, polyethylene, polypropylene, polyamide, polyester, polytetrafluoroethylene, or a combination of two or more of these materials.

6. A medical device as claimed in any one of claims 1 to 5 wherein said porous material comprises a non-swellable biostable polymer.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 3427

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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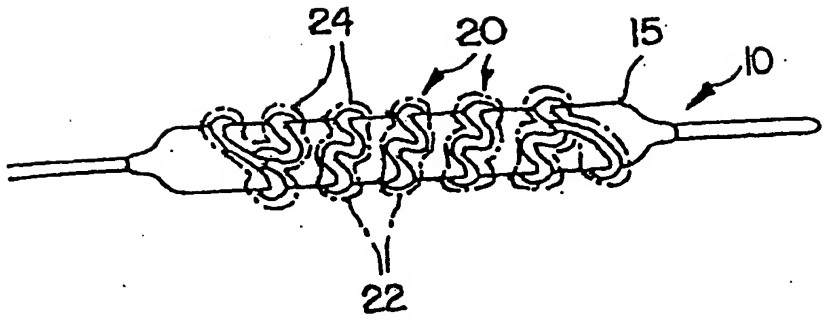

FIG. 1

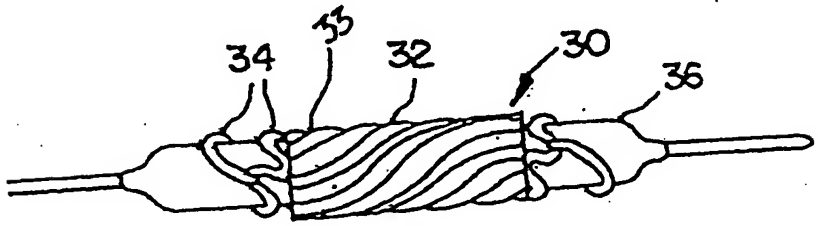

FIG. 2